

APR 17 2008

Appl. No. 10/749,119

Atty Docket No.: 286336.152US1/NOR-013CP2

Response to Office Action of 11/01/07

REMARKS**I. Restriction/Election:**

Applicant thanks the Examiner for rejoining Group IV claims (69 and 70) with Group I claims for examination on the merits. Claims 21, 22, 24, 26, 32, 33, 37, 44, 53, 56, 61, 63, 67, and 71-75 have been withdrawn as being drawn to a non-elected invention.

II. Amendments to the Claims:

Claims 19-26, 28-40, 42-44, 46-49, 53, and 55-75 are pending in this application.

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, 68-70 are under examination.

Claim 65 has been canceled without prejudice. Claims 19, 35, 36, 42, 66, 69, and 71 have been amended herewith. Support for the claim amendments can be found throughout the application as filed, *inter alia*, at page 28, lines 13-19; the paragraphs bridging pages 8-9; page 30, lines 11-15; page 31, lines 6-12 and lines 22-26 of the application-as-filed. Accordingly, no new matter has been added by way of this amendment.

Upon entry of the instant amendment to the claims, claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, 68-70 will remain under examination in this application.

III. Amendments to the Specification:

As requested by the Examiner, the status of each application in the first section of the specification has been updated.

IV. Claim Objection:

Claim 35 was objected to because LHRH was not spelled-out the first time it appears in the claim. (*see*, Office Action, page 4)

Claim 35 has been amended to provide the full form of LHRH. Therefore, Applicant avers that the grounds for this objection have been overcome. Accordingly, Applicant respectfully requests that this rejection be reconsidered and withdrawn.

Appl. No. 10/749,119
Atty Docket No.: 286336.152US1/NOR-013CP2
Response to Office Action of 11/01/07

V. Rejections Under 35 U.S.C. §112, Second Paragraph:

(a) Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, and 68-70 were rejected under 35 U.S.C. § 112, second paragraph, because the Office Action purports that the claim recitation "a mismatched donor" is vague and indefinite.

Without acquiescing to this rejection and solely to expedite prosecution, independent claims 19, 66, and 69 have been amended to recite, in relevant part, "MHC-mismatched donor."

(b) Claims 36 and 71 were rejected for reciting trademarks.

Claims 36 and 71 have been amended herewith to remove recitation of trademarks.

In view of the instant amendments, Applicant avers that the grounds for the rejections of claims 19, 36, 42, 66, 69, and 71 under 35 U.S.C. § 112, second paragraph, have been overcome. Accordingly, Applicant respectfully requests that this rejection be reconsidered and withdrawn.

Likewise, the rejection of claims 20, 23, 25, 28, 31, 34-35, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-65, and 68-70, which contain all the limitations of the independent claims upon which they depend, should also be reconsidered and withdrawn.

VI. Rejections Under 35 U.S.C. §112, First Paragraph, Enablement:

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, and 68-70 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly being non-enabling. (*see*, Office Action, page 5).

Applicant respectfully traverses this rejection for the reasons described below.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988) The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983).

Appl. No. 10/749,119
Atty Docket No.: 286336.152US1/NOR-013CP2
Response to Office Action of 11/01/07

The present invention relates in part to the finding that the reactivation of the thymus of a patient who requires an allograft transplantation will improve acceptance by the patient of that allograft compared with a patient whose thymus has not been reactivated. Once the thymus is reactivated, a new immune system is created, one that no longer recognizes and/or responds to antigens of the allograft. In other words, the allograft is seen as "self," and not as foreign.

The application as filed provides sufficient guidance to one of ordinary skill in the art to make and use the invention as claimed. For example, the disclosure at page 51, line 16 to page 53, line 6; page 61, line 3 to page 62, line 28; page 75, line 19 to page 81, line 13; Figs. 20 and 21; page 84, lines 2-28; page 88, line 24 to page 89, line 14 of the application as filed provides a sufficient disclosure to one of ordinary skill in the art regarding increasing tolerance in a patient from a graft from an MHC-mismatched donor as presently claimed. In this context, it is noted that the Federal Circuit has made clear that an applicant need not have actually reduced the invention to practice prior to filing. *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987). The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it. *Id.*

In addition, Applicant provides herewith an article from the Applicant's laboratory entitled "Enhanced Immune Reconstitution by Sex Steroid Ablation following Allogeneic Hematopoietic Stem Cell Transplantation," in Appendix A, which supports the instantly claimed invention. Specifically, Applicant points to page 7474, right column ("*Mice and HSCT; Surgical Castration*"); page 7476 ("*Castration before allo-HSCT results in an increase in thymic cellularity as well as thymocyte and dendritic cell numbers*"); page 7477 ("*Splenic cellularity is increased with more donor-derived peripheral T and B cells 28 days after castration and allo-HSCT*"); and page 7479 ("*Castration prior to allogeneic HSCT does not exacerbate GVHD and maintains GVT activity*") of the attached article. Applicant notes that the only difference between the sham castrated and castrated mice is the disruption of sex steroid signaling in the latter. The data in this article shows increased tolerance to the transplanted donor cells in the castrated mice,

Appl. No. 10/749,119
Atty Docket No.: 286336.152US1/NOR-013CP2
Response to Office Action of 11/01/07

because if the cells were not being "tolerated" the allogeneic cells would not have been detected at the time points examined at a higher level than in sham (non-castrated) mice.

In view of the foregoing remarks, Applicant submits that the pending claims are fully enabled. Accordingly, Applicant respectfully requests that this rejection under 35 U.S.C. § 112, first paragraph, enablement, be reconsidered and withdrawn.

VII. Rejection Under 35 U.S.C. §102(b):

Claims 19, 20, 23, 25, 28-31, 34-36, 42, 43, 46, 55, 57-59, 62, 64-66, and 68-70 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ghalie *et al.* (*Am. J. Hematol.* 42:350-3, 1993). (*see*, Office Action, page 8).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Ghalie *et al.* do not anticipate amended claim 19 and the claims dependent thereon, because Ghalie does not teach "administering cells from the MHC-mismatched donor to the patient, the cells being selected from the group consisting of stem cells, progenitor cells, dendritic cells, and combinations thereof; and providing the graft from the MHC-mismatched donor to the patient." Ghalie *et al.* do not anticipate amended claims 66 and 69 and the claims dependent thereon, because Ghalie does not teach "administering cells having the same histocompatibility as that of the MHC-mismatched donor to the patient, the cells being selected from the group consisting of stem cells, progenitor cells, dendritic cells, and combinations thereof; and providing the graft from the MHC-mismatched donor to the patient."

Because Ghalie *et al.* do not teach each and every element of the claim, Ghalie can not anticipate the instant claims. Accordingly, Applicants respectfully request that this rejection of claims 19, 42, 66, and 69 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Likewise, the rejection of dependent claims 20, 23, 25, 28-31, 34-36, 43, 46, 55, 57-59, 62, 64, 65, 68, and 70 which contain all the limitations of the independent claims 19, 42, 66, and 69 as amended, should be reconsidered and withdrawn.

Appl. No. 10/749,119
Atty Docket No.: 286336.152US1/NOR-013CP2
Response to Office Action of 11/01/07

VIII. Rejection Under 35 U.S.C. §103(a):

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, and 68-70 were rejected under 35 U.S.C. § 103(a) as purportedly being obvious over Mardiney *et al.* (U.S. Patent No. 6,863,885), in view of BBC News (December 1998), and Windmill *et al.* (*Tissue Cell*, 30:104-11, 1998) (*see*, Office Action, page 9).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

In this case, the combined references do not render obvious Applicants' amended claims because they do not teach or suggest all claim limitations. Specifically, the combined references do not teach or suggest "administering cells from the MHC-mismatched donor to the patient, the cells being selected from the group consisting of stem cells, progenitor cells, dendritic cells, and combinations thereof; and providing the graft from the MHC-mismatched donor to the patient."

Furthermore and importantly, the Office Action has itself conceded that:

it was still controversial in the art concerning the correlation between thymus reactivation and graft rejection. In fact, the art of record is replete with evidence contrary to what is now claimed. (*see*, Office Action, page 7, first full paragraph) (emphasis supplied).

Accordingly, given the state of the art described by the Office Action, it is clear that there would have been no motivation to combine Mardiney with the secondary references. Even if the combination were to be suggested (which is denied), as discussed above, all claim limitations have not been taught by the combined references.

Accordingly, Applicant respectfully requests that this rejection of independent claims 19, 42, 66 and 69 under 35 U.S.C. § 103 be reconsidered and withdrawn.

Likewise, the rejection of dependent claims 20, 23, 25, 28-31, 34-36, 43, 46, 55, 57-59, 62, 64, 65, 68, and 70 which contain all the limitations of the independent claims 19, 42, 66, and 69 as amended, should be reconsidered and withdrawn.

Appl. No. 10/749,119

Atty Docket No.: 286336.152US1/NOR-013CP2

Response to Office Action of 11/01/07

IX. Information Disclosure Statements:

Applicant notes that four Information Disclosure Statements (IDS's) submitted on August 6, 2004, November 2, 2004, January 20, 2005, and August 12, 2005, respectively, have not been initialed and returned by the Examiner.

Accordingly, Applicant respectfully requests that the Examiner initial and return these IDS's with the next Office Action.

APR 17 2008

Appl. No. 10/749,119

Atty Docket No.: 286336.152US1/NOR-013CP2

Response to Office Action of 11/01/07

CONCLUSION

Upon entry of this amendment, claims 19-26, 28-40, 42-44, 46-49, 53, and 55-75 will remain pending in this application.

Applicant petitions for a three-month extension of time to respond to the outstanding Office Action. Please charge the requisite fees to our Deposit Account No. 08-0219. No additional fees are believed to be due in connection with this correspondence. However, if any additional fees are due, please charge the fees due to our Deposit Account No. 08-0219.

If a telephone interview would advance prosecution of the application, the Examiner is invited to telephone the undersigned at the telephone number given below.

Respectfully submitted,

Dated: April 17, 2008

/Ann-Louise Kerner, Ph.D./
Ann-Louise Kerner, Ph.D.
Reg. No. 33,523

WILMER CUTLER PICKERING HALE AND DORR LLP
60 State Street
Boston, MA 02109
Tel.: (617) 526-6192
Fax: (617) 526-5000